Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Member Discussion

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DR. WAGNER: So let me remind everybody what we are doing. We are moving now towards the broader, the broader issues of medical countermeasures. Imagining that one of the things that we can contribute in addition to the specific response about the anthrax challenge that we were given by Secretary Sebelius that we can respond more broadly with a framework that can be used to evaluate MCM issues, medical countermeasure issues, and opportunities going forward and so we have had committees working on this. You have been heading subcommittee A? No? You were just given the responsibility of doing--so what we are going to do to remind the commissioners, and those in the audience to let you know, is we are going to receive-- the commission is receiving a draft proposed framework, evaluation framework. We are mostly, this afternoon, we are in the mode of listening and mode of making sure we understand what is being recommended to us as a commission, so this does not stand as our recommendation going forward just yet and then tomorrow, we will have a great deal of opportunity to make it our own. So let's start first, Christine, you are going to present and then Dan, you are presenting as well. So let's start with you Christine.

DR. GRADY: So I am a member of subcommittee A and those who are on that subcommittee can also jump in. I think the idea was to sort of talk through some of the issues that are in the draft so that we can begin to grapple with them and then discuss them today and tomorrow as Jim already said. So, briefly, we are assuming there is some foundational ethical principles that guide research with children and these are, these principles are reflected or reflected in the current regulations in subpart D. So one of those principles is there an important value in identifying safe and effective ways to diagnose, prevent, and treat conditions that affect children through research and identifying those ways through research. Some might even say there is a moral imperative, but we can at least say there is a value to identifying ways to treat children. Second, there is a general prohibition against exploiting people in research, including children, and one way that the current draft, um, because to talk about that, which has already come up this morning, is that there is an ethical norm and necessity that a democratic society not use individual children as means only to the ends of others or as only means to the ends of others. Another foundational principle is that, again reflected in the regulations, is that greater than minimal risk research with children should be done only when the participants stand to benefit directly, that the children stand to benefit directly, with two exceptions, and we have

heard about these exceptions already today. The first one is the case where the research risk is a minor increase over minimal and the research is likely to yield generalizable knowledge of vital importance to understanding or improving a subject's specific condition. That is what is reflected in 406. And then the second exception to greater than minimal risk research with children that is not of benefit to them is the case that we have been asked to consider and that is the case of research that currently under the regulations requires a separate process and requires research to present a reasonable opportunity to further the understanding of a serious problem affecting children, including healthy children, and that has certain conditions related to risk and parental permission and assent and I am going to talk about in a second. So the National Commission in the 70s anticipated the possibility of exceptional cases where children might be asked to assume more than minimal risk in the case of a serious problem that might affect all children as a group, including healthy children and the current regulatory framework requires that the Secretary of HHS informed by a national panel of experts determine that such research meets all of the following conditions in order to proceed and I am going to read the three conditions. The first one is the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The second one, the research will be conducted in accordance with sound ethical principles and the third one, adequate provisions are made for soliciting the assent of children and the permission of their parents and guardians as set forth in other parts of the regulations. So I think we started as a commission by recognizing that this is very helpful guidance, but it is very broad and thought that there was a need to specify further those current criteria, especially in order to address the particular complexities of medical countermeasure research in children. So we are working on a framework to clarify each of those conditions a little bit further or to make them more specific and more operational. So one part of that will be to specify further what constitutes a reasonable opportunity. Another will be to specify further what is a serious problem, including that it has serious--a problem that might have serious consequences and a mid to high threat level or likelihood of exposure in the context of MCM. The third part of this is specifying that the Secretary of Health and Human Services be transparent in how that determination was come to. In other words, how the threat was calculated, how the problem was deemed to be serious, and the rationale for a study that exposes children to risk for the purpose of that serious problem. With respect to trying to think through and further specify the, I want to

get the right words, the sound ethical principles that are already written in 407, we came up with four ethical conditions to ensure that children being tested, who don't stand to benefit from their participation in the research, are respected as persons and in accordance with ethical norms are not used only as means. One of those is to talk about the threshold of acceptable risk and adequate protection from harm. So, this has been, in my view, actually the hardest one, but we have talked about it quite a bit and we have a little bit in the draft right now that sort of may get us started anyway. So one way that we have talked about it is in general, even though the risk is greater than minimal, or it wouldn't get into this category, there still has to be low or limited in some way. There needs a limit on the risk. Another way we talked about it is a level of risk that wouldn't demean the dignity of children as human persons who ought not to be subjected to undo risk merely for the benefit of others. Um, we also recognize that research should only precede, this kind of research should only precede, when without it children as a class would remain vulnerable to the possible serious harm and only by going forward with the research would the potential for serious harm be mitigated. So it is a way to compare the two. And then we talked about whether or not the level of risk should be described as no more than a minor increment over minimal risk, whether that should be a sort of standard or whether there might be two categories. One is that in most cases, even in this 407 bucket, the level of risk would be no more than a minor increment over minimal and then in some exceptional cases, in this bucket, there might be room for minor increase over minor increase or whatever as John has been talking about and that might be the case of, I don't know, a national emergency, some kind of immediacy, some kind of extremely serious problem, well all, of course, left to be determined what those mean. Um, just one last comment, as everybody knows and has been described already again today, the way the regulations, the current regulations under 45CFR46 subpart D are laid out, it is sort of a stepwise progression of protections based on understanding risk, so 404, to reiterate is research is permissible in children if it is no more than minimal risk to the children in the study. 405 is research is permissible in children that is greater than minimal risk if it presents the prospect of direct benefit to those children, the children in this study. 406 allows research, which is a minor increase over minimal risk in children, if it is vitally important for understanding or ameliorating the condition, the subject's condition and it is no more than a minor increase over minimal risk. And so all of those categories are thought of as adequately protecting children from harm under the circumstances and so the filling in that we have been

trying to do is how do we make 407 specific to adequately protect children from harm in a circumstance where it is greater than minimal risk, no prospect of benefit, and healthy children were or serious problem of children as a class. I think that is all I was going to say.

(Inaudible)

DR. SULMASY: Yeah. Sure. I was just going to begin by kind of my own take on framing some of what we have been doing here before I get into the specifics. I think in some sense we have got on the one hand, event concerns, um, and then on the other hand, research concerns. In both cases, um, everybody is motivated by wanting to protect children, right? So the event concerns we hear mostly from the security community and the research community and we recognize the children are especially vulnerable to environmental harms, even when you measure particle intake per pound or something like that, whether it is natural or by acts of terror, right, and we want to protect them and that's sort of driving one set of concerns and the other are research ethics, research ethics concerns, mostly from the pediatric research ethics community, says children are vulnerable and especially susceptible to abuse in research and we want to protect them from that as well, but I think in some sense all of this is aiming at trying to protect children. Our challenge is to satisfy both sets of concerns at the same time to the best of our ability. Given what Christine said, subgroup B sort of takes it as a conditional, sort of if we are to determine that there is some sort of medical countermeasures study that would be but worthy of being undertaken, what are the sort of conditions under which we would undertake that kind of an experiment and so anthrax vaccines are just one particular example of that. Um, the low hanging fruit, as I call it, in some ways I think reiterates a lot of just what's out there in basic pediatric research, that it has got to be scientifically necessary and, again, we may want to put twists on this, you know, that there would be no possibility of study in a less vulnerable population, that we really can't simply extrapolate from adults, that it is important and it is a well-formulated scientific question that is being asked and it is about the welfare of children that is the concern. Um, secondly, where it is possible and appropriate that it be tested and found safe and effective in adults before trying it in children. This is something that we would think. And, if not, at least do the best animal experiments and other kinds of extrapolations that could be done. Third, there is a sort of a pithy quote here that the expected benefit to children as a class must be sufficiently greater than that of the most beneficial alternative that does not impose greater than minimal risk without the prospect of direct benefit. Um, to unpack that, I guess in

some ways I just sort of say that what is being tested has a realistic prospect of being better than anything that is already out there. I mean that is the way we want to say it and there is known--and it is known to be at least as, um, as safe for children. Um, for example, for instance, if antibiotics are safe and at least somewhat effective for bioterrorism threat X, whatever it is, and a new vaccine offers no prospect of a greater benefit then there probably shouldn't be a reason to proceed with the studies. That is what I think that means.

DR. FARAHANY: Can I just ask one question on that, which is, um, has the subcommittee deliberated on what would count as a greater benefit. I mean is like greater likelihood of compliance a greater benefit. Is it just a greater therapeutic benefit? Does it have any greater definition than that?

DR. SULMASY: No. We hadn't gotten into, to the best of my recollection, a lot of detail on that, but that is more--again, this is just sort of a framework that we are working with and we need to unpack more of this certainly.

DR. WAGNER: What I think is a friendly amendment that certainly ought to be taken under consideration, we know that Cipro will work, the question whether it will be compliance to taking Cipro for six weeks.

DR. SULMASY: Correct. So I think that those kinds of considerations, um, the kinds of things we heard--again, if you want to get into specific examples here about the duration of the, of the threat, the possibility of, you know, something like anthrax spores hanging around for a long time, etc. All of those things would be details that would be filled into that, so I think that is a friendly amendment.

DR. WAGNER: This is a practicality issue as well as a scientific issue.

DR. SULMASY: Yes, yes, yes. Well, I think you can make the--doing health services research about ethical issues. I know that you can do scientific studies of the practical concerns too, so it is not, not all exclusive. Um, um. Fourth, um, again, low hanging fruit that

the research is well-designed, that it is going to answer the research question that is being posed, um. Dr. Fleischman for instance suggested that it be adequately powered. We have got to have all those sorts of concerns. Um, fifth, that it be ethically designed, right, that it minimizes the risks wherever it is possible to minimize the risks, that there be monitoring, that there be safeguards, that these sorts of things be built into the, um, into the protocols. Um, sixth, um, and we heard some of this in our testimony that subjects be selected fairly, um, um, not for convenience alone and that the children enrolled should be at least as likely to benefit as those who do not. Um, um, for example, if we think that children in a juvenile detention center are, you know, an unlikely target for an anthrax attack then maybe they are not the first people you go after to be the people that you are going to study in the study. There might be other reasons why you wouldn't want to make them the first people either, but that kind of consideration. Um, there was some consideration to inviting those with some plausible chance of direct benefit to be the kinds of persons who, children, that would be enrolled. Um, you know, it is hard to really, um, say in a low likelihood, high impact event who those exactly would be, but, you know, you can begin to sort of say that, you know, if there were children-we have heard these sorts of things before, children who work and live on cheap farms or something might be persons. Children of first responders, etc., as we have heard something of here who might have some chance of benefit, although, again, we have heard the counterarguments that it cuts both ways, they may have already been at risk. Um, children, um, um, and then justice concerns in general. The children enrolled in the trial should have access to the intervention in the event of an incident. This seems to be again a very important concern. There be some kind of fair plan for distribution, um, and access to the better, uh, to a better intervention should one become available, so simply the fact that you've gotten this anthrax vaccine, if we find a better one later and you volunteer, it doesn't mean that you are stuck with the old one, that you have access to the newer stuff as well. Um, again, concerned with justice that there be no undo inducements. Um, you might pay for parking, etc., but you don't want to have, you know, large sums of cash that might be considered exploitative, um, um, or too much appeal to patriotism in ways that might be exploitative and that there be no, as I have labeled it, "pay for performance requirements that access to the intervention in the event of an incident is contingent upon your participation". You don’t want to make certain that people think that they don’t get access to the intervention if there is an incident, um, if they haven't participated. And then, as we have heard before, um, the

subcommittee felt that there should be a system of compensation for injuries directly related to participation. Again, the appeal here is absolutely to the altruism, um, of those who would participate, um, and um, there is no direct benefit to the individuals and certainly the numbers as we have heard in these kinds of things are likely to be small, so while at least within this sphere we have felt pretty strongly that there should be some system of compensation for, um, direct injury related to participation. Um, and then, um, a set of concerns about accountability and transparency, um. We felt that the HHS Secretary must provide public justification for the research and an accounting of the risks and benefits and detailing the procedure for consent and assent and their justification as well, that all of this ought to be made public and as we heard importantly this morning and again this afternoon that community engagement is critical for this kind of research to take place, that it be a public and participatory process, um, that community engagement and education maybe is the first medical countermeasure, um, because it would be all well and good to do the study if no one uses the vaccine, so this is important. Um, and then finally, um, to give a special emphasis in this kind of research to the assent of children who would participate. Again, this is sort of a no-brainer. We think about this in pediatric research more generally, but in this case, parents would be giving permission or sort of formal consent, but the child's assent is absolutely necessary. If the child says no in any form that it really shouldn't be permitted for them to be enrolled and then as we heard this morning, certainly that we would endorse that it be developmentally appropriate form of ascent. So those are the kinds of considerations for the conduct of the research that subgroup B was concerned with.

MS. ALI: Dan, is there anything mentioned in here with regards to--

DR. SULMASY: Microphone.

MS. ALI: Oh, I'm sorry. In regards to distribution channels of how this would be--because you have all this done and it is one of the things that was brought up I think by Dr. Fleischman about, you know, they are not--or maybe it was Dr.--well somebody--about right now they are just setup for the antibiotics, oh no, it was the gentleman over here.

DR. SULMASY: Bruce Lockwood.

MS. ALI: Yeah. And there is no setup for the distribution of the vaccine itself and I think when you are doing this, I think it is very important for us to say something about that because you may have this already to go, but if you don't have the distribution in place it is just a catastrophe waiting to happen.

DR. WAGNER: I mean there were actually several, I thought, um, ideas brought forward, I don't know the merit of them, for post-event. One was that, distribution and access around fairness, but the other was insisting on some form of monitoring protocol post-event that also could--

DR. SULMASY: Yes, yea.

MS. ALI: I am talking about actual distribution of the vaccine itself.

DR. SULMASY: You are right that we gave--we had some discussion of sort of post-event, um, considerations before you would even do this kind of, of research and certainly while we didn't say it explicitly I don't think in here--

MS. ALI: I think we touched on it.

DR. SULMASY: We probably ought to mention again, um, it is not worthwhile to undertake this kind of research if we don't think that we are going to have again public participation, distribution, infrastructure that assures that people get it, um, that there be monitoring, um, afterwards. I think all of that could, could deserve better emphasis here because, again, that is not going to happen then it is probably not worthwhile starting to expose children to the risk at all so.

DR. WAGNER: Other questions or comments, clarification on the framework? Yes, MS. ALI.

MS. ALI: I want to ask because I am not clear anymore, I know we are putting together this framework, not just for AVA, but for pediatric research and MCM research, but are we actually going to make a recommendation as to whether or not this research should take place for anthrax?

DR. WAGNER: We are imagining two outcomes from the committee, two products of the committee. One is this framework and it would be terrific if by tomorrow's discussion, through tomorrow's discussion, that guides are staffed to help us so that between now and the end of the year that is really firmed up so that in our meetings after the first of the year, we might focus on applying that framework for recommendation on the anthrax. We have been asked to opine on the anthrax piece, so we have to do that. So thought is to have those two deliverables. Does that make sense?

MS. ALI: Yes, it does. I thought that was it, but it seems to me it becomes more difficult or it seems like there are these stumbling blocks in front of us since there has not really been adequate research done on adults.

DR. WAGNER: Yeah. Getting back to the anthrax piece you are talking about?

MS. ALI: Right.

DR. WAGNER: Right. That I think we want to hold and it will be one of the ways we test this framework and what is missing before you could, you could make a definitive recommendation. Yes.

DR. ATKINSON: It almost seems to me that I think we need to make a recommendation on anthrax, but still a 407 panel to me is who would really decide it, so--

DR. WAGNER: Good point.

DR. ATKINSON: So the framework should help them and we can say what we think, but refer it if you will or at least think about doing it that way.

DR. WAGNER: I guess specifically we were asked to offer an opinion coming out of the prior commission's recommendation, um, about the ethical dimension, not just the scientific dimension, but the ethical dimension of going forward and we owe that opinion. That is a good distinction.

DR. ARRAS: Barbara, you are right. You're going to need a protocol in front of you to really get a grip on the actual risks that children are going to be exposed to so.

DR. FARAHANY: And the purpose of the study.

DR. WAGNER: Yes. And the purpose--

DR. FARAHANY: And the purpose of the study, not just the risks.

DR. ARRAS: The whole nine yards, yeah.

DR. WAGNER: And, in fact, in a sense, we would be providing one piece of it. We would be providing the ethical dimension of that. That is what we have been asked to provide, not to make the decision on whether or not testing should go forward.

DR. ATKINSON: And if I can ask another question. It is one that I have asked before, but maybe somebody could give a primer on on exactly about the individual children as means only and--

DR. WAGNER: There you go.

DR. ATKINSON: And exactly what that, that discussion is and how we should think about that as a framework or not.

DR. WAGNER: This is the Kantian question.

DR. ARRAS: Well, okay.

DR. WAGNER: We are all looking at you John.

DR. ARRAS: Um, Nietzsche described Kant as a philosopher who said very common sensical things in a language that common people couldn't understand. (Laughter). Okay, well, you know, so Kant is famous for having said that human beings uniquely in the world, in the cosmos, are uniquely valuable because of our ability to reason, you know, and to engage in rational agency, right, to make choices geared, you know, dictated by reason. So this gives us a kind of unique value, as opposed to everything else that is just stuff or just a means to an end, okay. So Kant makes a distinction between treating people as they are, as ends in themselves, respecting their personhood, respecting their ability to make choices, and just using them like you would use a thing, okay. So the usual test for that, you know, is the maxim that you should never, you know, use somebody for an end that they couldn't or haven't consented to, right. So one way you know that you are just treating somebody as a means to an end. You are just doing stuff to them without their consent. That is a major Kantian test, alright. So, as I was saying before at lunch, you know, this gets us pretty far in a number of cases like, you know, where you really do some violence to somebody or you lie to them or you act paternalistically toward them because there you are really threatening their, their rational agency by your action, right. So I think what we are getting at here and we will have to debate this more tomorrow is whether that kind of principle is useful for us in this context, right, okay, because children certainly aren't rationale agents. Some of them can given ascent, right, but they, they, for the most part, can't really give genuine consent, um, so the Kantian terminology, I think, you know, I think there is a desire to use that to indicate that you just shouldn't treat people like stuff, you know, you shouldn't treat people just, just as mere means to, you know, your ends regardless of their interests or their desires or their consent. Does that help?

DR. ATKINSON: It does.

DR. ARRAS: Okay. I mean, but the one, the one issue that we probably should discuss tomorrow, Dan and I had an interesting discussion in the hallway about this earlier, is whether that kind of language at the masthead of our framework document is really going to be helpful because the problem that I see here is we don't really know if we are treating somebody as a mere means to an end until we know what level of risk is acceptable, right. Okay, so, so if that is the case then the principle of never treating somebody as a means to an end isn't really doing any work. It is the ribbon you wrap around a decision that a risk is too great.

DR. WAGNER: Actually, I've got Dan that wanted to respond first. Can you hold Christine for a second?

DR. SULAMSY: Yeah, just to give you a sort of history and how I think it got to the position it did within subcommittee B is that it came out of this sort of trying to look at the risk, um, and one of the things that we said, well we shouldn't tolerate a level of risk that is exploitive, um, um, and then exploitation raised questions about dignity and dignity got us to this sort of Kantian language in which we said, well we shouldn't treat children merely as means because this is the, this is the basic problem with, you know, the ethics of research if you simply do research on children so that, for instance, as we were saying before, adults will benefit, that seems to be the kind of instance in which that maxim would be violated and then it got elevated to where it did, so that is how it came, you know, through in our deliberations. We can talk tomorrow about, you know, whether it has any get real value or not. I actually happen to think it still does, although we might want to add in the Kantian language of treating them as ends in themselves, um, so I think that helps to capture a little bit more of what we want, um, in addition to never is means only, but we can talk tomorrow.

DR. WAGNER: I've got Anita, then Nita, then Christine.

DR. ALLEN: So I think what we ultimately want is to offer a report that doesn't come across as being viable only within one particular metaethical, theoretical framework so we have to be careful about being too specifically Kantian in our approach, so I would suggest that

we, um, throughout the report speak broadly in terms of not harming children, in terms of not exploiting children, in terms of, um, not using children in ways we don't use adults, and, furthermore, in recognizing the special vulnerability of children. We in any case take special effort not to use children at all. So I think that combination of, of, um, of perspective is what we want to have. If we just narrowly speak in terms of not using children as means only, it might just send the wrong signal. It may seem that we are not even contemplating the possibility that some ethicists might not, as one of our panelist this morning was saying, she comes from a care perspective in ethics, not a Kantian perspective, people they come from Aristotelian or from utilitarian, we don't want to exclude anyone who is trying to look at these issues ethically by adopting a rigid Kantian formula, but I personally respond very favorably to Kant's categorical imperative that we always treat humanity whether in our own persons or the persons of others as ends themselves, never as means, but it is a very particular way of thinking about what it means to be a good person, right, so we have to be inclusive and not let particular categorically imperative totally control the way we present our ideas to the public.

DR. WAGNER: Nita.

DR. FARAHANY: So I just have--I have a series of questions actually about clarifications that I am hoping, you know, you both can help guide me on, so I will start with, I will start with one, and I am going to go by the numbering of the big one and then the sub two. So starting with one, which is the risk calculation, so this is 1,2, A and B and this specifies the type of problem proposed seeks to qualify a sufficiently serious problem and A is the consequences of exposure has to be likely and serious. It is B that I am struggling with a little bit. So B says probability of threat or exposure. The dimensions include the threat of an attack or the likelihood of a naturally occurring outbreak. To be a serious problem, the probability of exposure must be mid to high or least not low or inestimable. And that doesn't mean a lot to me, except that some were greater than inestimable, um, and I am having trouble kind of wrapping my head around what is that, right? So are we really saying that as long as it is above inestimable, and by that we mean that somebody can estimate it, not just that we have access to that information, um, that, that counts or that it really does need to be a mid to high level

probability in order for it to satisfy the serious problem, even if the magnitude was quite high. So either of you who could clarify.

DR. ARRAS: Nita, could I add a codicil to your questions?

DR. FARAHANY: Yes. And this is just one, so I have got three question (laughter).

DR. ARRAS: And maybe we are getting too far into the weeds here, Jim. I don't know--

DR. WAGNER: If this is--if what we can do is frame up the kind of question we want to debate tomorrow, I think that is well within what we are doing now.

DR. ARRAS: Okay, okay.

DR. WAGNER: So we can mark that, yeah, so if you could help us--

DR. ARRAS: I just had a question mark with regard to naturally occurring here because, you know, to the best of my knowledge, this sort of naturally occurring anthrax attacks are pretty limited--

Dr. FARAHANY: Right.

DR. ARRAS: Right. I mean I wouldn't think that they are the sort of thing that would justify putting children in a greater than minimal risk to get answers to, so I am

(Inaudible)

DR. WAGNER: Yeah, but this is the broad--remember this is the broad framework.

DR. ARRAS: Yeah, okay, okay.

DR. WAGNER: So I guess pandemic flu.

DR. ARRAS: So pandemic flu might. Yeah, okay, I withdraw the codicil.

DR. FARAHANY: So this just may be something that we want to debate tomorrow, but I am just kind of putting it out there. This seems like something, unless we have greater clarification on what that means right now.

DR. WAGNER: Christine.

DR. GRADY: No, I was just going to respond to Nita in exactly the way that she just suggested that, you know, this is part of our subcommittee and the question really at hand was how do we think about what constitutes a serious problem? How do you describe that? And so these are just possible ways to describe it, but I think you are absolutely right, that sentence, we maybe have to decide which one do we mean of those two and not both in the same sentence because that doesn't make any sense.

DR. WAGNER: And also here, the committee is thinking about mid to high versus low or inestimable. I hope we can have some more conversation.

DR. FARAHANY: So maybe I am just marking that for conversation.

DR. GRADY: It is a good conversation to have.

DR. WAGNER: Where is that between your nose and your hands when you are now talking about risk?

DR. FARAHANY: Okay, so a couple more. The second one is, again this is a subcommittee A thing, so this is--no this is not. This is under number 2, number 1, so this is the threshold of acceptable risk and adequate protection from harm. Um, so, in the second full paragraph there, which is research within this framework must involve a level of risk that would not demean the dignity of children. Further down that paragraph, we have that such research may only proceed when without a children as a class, many or all would remain vulnerable to the possible serious harm and only by going forward with the research, the potential for serious harm would be mitigated. Its that sentence that I am wondering what we mean by because I can imagine in the example of anthrax that there may be other ways for the potential serious harm to be mitigated, both with existing countermeasures, as well as ones that could be developed in the future and so I am not sure if that is meant to be such a bright line threshold or if it is just simply overstated as to what it is or if it is really meant to be a--if there is any other means possible then we simply don't go forward with research, um, so something for us to discuss. And the last one is the fair subject selection and this is just a point of clarification, so, um, again, using the example of anthrax, which I recognize this is a broader framework, so imagine that we test on a military base for example and it happens in North Carolina, because that is where I am, so I will use that as an example, and an attack happens in San Francisco, I would suspect that the right answer is that children in San Francisco would be first in line to receive--

DR. GRADY: Absolutely.

DR. FARAHANY: You know, anything and the children who are in, you know, in North Carolina who are not exposed might be deprioritized relative to the children who are actually in line for attack and so some of the language in 2.2 and 3 seems to me to prioritize those children even if it isn't appropriate or necessary given other response initiatives and so I just want us to mark that as a point of discussion to make sure what do we mean by fair subject selection? What exactly is it that we are saying, that these children should not be any lower priority and not that they should be the first priority irrespective of other considerations that we might take into play, like the immediate threat that is posed to them.

DR. WAGNER: Good. It looked like, John, you were about to say something.

DR. ARRAS: Oh, no. I'm--

DR. KUCHERLAPATI: (Inaudible).

DR. WAGNER: Yes, Raju.

DR. KUCHERLAPATI: So I just want to make a comment about, you know, maybe we need some preamble--

DR. WAGNER: Yeah.

DR. KUCHERLAPATI: And that is that much of the discussion is based upon the view that any sorts of countermeasures research could be potential be harmful to children, but there is actually an opposite side to that coin. The goal for society as a whole is to try to keep all of the population, including the children, to be as healthy as possible, right, and that you have to take whatever measures are necessary to be able to keep them healthy and sometimes if the measures that are necessary to keep them healthy might include some level of risk, so you cannot--I mean there is no enterprise, human enterprise, that is completely devoid of risk. And so one has to be willing to accept some level of risk and I don't know what that level of risk is and so one of the points that I want to make is that if you actually don't do any research on children--

DR. WAGNER: (Inaudible)

DR. KUCHERLAPATI: Then actually you might be causing more harm to that group of individuals then, you know, by doing the research, so there has to be clearly a balance between these two, but we don't want to sort of start out in saying that, you know, this is a terrible thing to do and we are trying to minimize, you know, the risk to people without recognizing the importance of, you know, measures that are required to be able to keep that population healthy.

DR. WAGNER: Dan, do you want to respond to that?

DR. SULMASY: Yeah. Raju, that was exactly the point of the sort of general framing I tried to do at the beginning of my comments to say there are event concerns, right, about protecting children from this and then scientific or research concerns protecting children from harm in research. Both sets of concerns are about protecting children and we have got to strike the right balance.

DR. KUCHERLAPATI: I am not talking about either one of them.

DR. SULMASY: No?

DR. KUCHERLAPATI: I am talking about something beyond that. The first principle is that you want to be able to keep children healthy.

DR. FARAHANY: Right. So I take, Raju, what you are saying is there may be an ethical principle of that we have a duty to actually, you know, a duty to do testing to safeguard children under certain circumstances and that we should consider--

DR. WAGNER: All of the population.

DR. FARAHANY: Right.

DR. GRADY: I think I tried to say that in the beginning because, I mean, some of it says there is a value to it and I said some would argue it is a moral imperative, it is a moral imperative to do the research.

DR. WAGNER: We ought to debate that tomorrow.

DR. ARRAS: Raju, another helpful source might be I guess it was the Institute of Medicine report on public health ethics, right, where they just spelled out very clearly at the

beginning that the goal of public health is to foster conditions that keep the population healthy, right, so. That is a place to look.

DR. WAGNER: That was an IOM piece?

DR. ARRAS: Yeah.

DR. WAGNER: I don't remember that. Has that been in our reading? Has that been in our reading?

DR. ARRAS: I don't believe so. George Benjamin could quote chapter and verse.

DR. WAGNER: I'll bet. I'll bet.

DR. SULMASY: Just quickly then, maybe what you are actually saying, which I didn't think was different from what I was saying is more principle that we have elucidated before of public beneficence, right, and particularly towards children in this case.

DR. KUCHERLAPATI: In other words, taking positive actions could be in some instances be beneficial?

DR. WAGNER: Yes.

DR. HAUSER: Could we in some instances?

DR. FARAHANY: Beneficial.

DR. WAGNER: Other thoughts--look at my watch here. Other thoughts? Yes, MS. ALI.

MS. ALI: We talk about, um, and we talked a lot about this in subcommittee B, about assentof children who can give assentand consent of parents, but given the testimony today with regards to the current framework of informed consent, is there anything that we want to see as a commission that would elaborate on that?

DR. WAGNER: Say that again. You mean in this framework?

MS. ALI: In this framework because they didn't feel that what we have today is adequate, which may be true. Um. I am not suggesting anything either way, I am just posing the question.

DR. WAGNER: That is good. Well, I have got about a half a dozen things that should keep us busy tomorrow and that is before we really dig in. Yeah Barb.

DR. ATKINSON: I have another one. The community engagement piece they spoke very eloquently and that needs to be expanded here and we can talk about that tomorrow too.

DR. WAGNER: Good, good.

DR. ARRAS: Beyond hand waving.

DR. WARGNER: Rumor has it--yeah Dan.

DR. SULMASY: Just another comment that I think we don't say anything about the question that we discussed a little bit this afternoon about, um, what could possibly be the justification for a parent enrolling a child in such a study to begin with at all, um, in terms of the sort of values that at least some people would have of altruism and contribution to the public good and we ought to at least--what we have here is a framework for protecting children, but we haven't said anything--

DR. WAGNER: So you are saying we should acknowledge--

Dr. SULMASY: Acknowledge the possibility--

DR. WAGNER: Different motivations.

DR. SULMASY: That there would be ethically reasonable motivations for parents to, um, engage on occasion within a proper structure of protection so that they don't go too far, um, to allow the children to participate in such research.

DR. WAGNER: Got it. Christine.

DR. GRADY: I think we need more conversation about the notion of what is a reasonable opportunity because we--it is part of what is in the 407 guidance, um, it says a reasonable opportunity to further an understanding, prevention, or alleviation of a serious problem and we have already talked about, you know, trying to figure out what a serious problem is and I think a lot of the discussion today made me think, you know, we believe that the possibility of a, um, threat with chemical or biological or nuclear weapons is a serious problem, but that doesn't mean that every research question is a reasonable opportunity to further understanding of how to solve of it and so how do we put those two things together?

DR. WAGNER: You know, it is interesting, there is a whole science of risk management as you know, which tries to weight those things, the seriousness, the problem, and the likelihood that it will occur and, um, that may be a place for us to get a little a guidance as well.

DR. SULMASY: Another thing that came up in our discussion today that I think might be helpful addresses, I guess, the second of Nita's concerns is that you could see that we were struggling with what the reasonable risk would be in terms of research risk. Um, exactly what would a modest increase or minimal increase over (laughter), over minor increase and minimal risk look like and that we thought that struggles to make--first of all, we have no

quantitative data in which to say that. Second, we struggled here, and you can see as others have, to do something in which we try to define necessary and sufficient conditions and have an air tight definition. Maybe the best that we can do is something that would be stipulative and sort of point out the kinds of examples of things that we would think are within the bounds of what this could actually mean and what would be beyond it, you know, somewhere between, as a I quipped at lunch, you know, breathing and death, you know, that there has got to be a sort point in there we can sort of make, at least a list of the kinds of things, as Dr. Fleischman started to do, that I think would be helpful to a 407 committee to actually begin to think about these kinds of things.

DR. WAGNER: One of the things worth conversation tomorrow would be the degree to which we want to have this too laden with stipulative approaches. Um, I have a certain reluctance to that unless it is just absolutely sort of last resort and even if it is, how would be exercise it for this specific example of anthrax? I can't tell if you are no or yes on that.

DR. GRADY: I think it would be really hard because as we have discussed and people have said, you know, risk is probability and magnitude and reversibility and duration and all kinds of other things and, you know, even in a very minimal risk procedure, there is a remote sometimes chance of death, so.

DR. SULMASY: You could at least stipulate the harms. You couldn't stipulate necessarily the probability of those harms, right?

DR. WAGNER: That is correct, the seriousness, the actual seriousness question. Still at the end of the day, I think we have been asked a very specific question about the ethics of one particular problem that we need to pine on. Lisa, you and your staff have all these written down?

(Inaudible)

DR. WAGNER: I have at least half of them written down and we will look forward to reconvening tomorrow. Thank you all for a very productive day and we thank all of our guests for bearing with us and for the several questions you submitted. Thank you.

(Applause)